Effect of preoperative delay on prognosis for patients with early stage non–small cell lung cancer

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Objective: Screening for lung cancer will discover many nodules of indeterminate pathology. Observation has the theoretic risk of permitting dissemination of a localized cancer and worsening prognosis, whereas immediate evaluation of benign conditions generates morbidity and cost. This study was conducted to assess the effect of delay in surgical intervention on survival for patients with early stage non–small cell lung cancer.

Methods: Records for patients with resected pathologic stage I and II non–small cell lung cancer (1989-1999) were abstracted for patient age, race, sex, medical history, date of presentation, date and type of surgical treatment, pathologic stage, and date of death or last follow-up. Kaplan-Meier survival analysis was performed to test for the effect of delay (time from presentation to surgical intervention) on survival.

Results: Eighty-four patients were identified. Median age was 66 years, median preoperative interval was 82 days (range, 1-641 days), and median follow-up was 3.3 years (range, 5 days-11.9 years). Median survival was 3.7 years. Overall 5-year survival was 40%; disease-specific 5-year survival was 63%. Log-rank analysis of the effect of delay on overall survival generated a *P* value of .54, with an estimated hazard ratio for a 90-day delay of 1.06 (95% confidence interval, 0.87-1.30).

Conclusions: For this population, we were unable to detect a significant effect of delay on prognosis. Although these results suggest that the risk of judicious observation of indeterminate pulmonary nodules might be low, the 95% confidence interval is broad. Larger sample sizes are needed to reach definitive conclusions.

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GTS

Renewed interest in lung cancer screening has led to the discovery of indeterminate pulmonary nodules in a large number of patients who are at risk for lung cancer. Management of these patients depends on knowing the risk associated with observation of cancerous lesions, but there is little evidence to help us understand the true effect of delay on prognosis.

Prompt evaluation and resection are the cornerstones of therapy for patients with a clinical suspicion of early stage non–small cell lung cancer (NSCLC).[1] Delay raises the uncomfortable specter of a lost opportunity for cure. Improvements in diagnostic studies, such as fine-needle aspiration cytology and positron emission tomography, tempt us with the prospect of a quick, less-invasive diagnosis, and the threshold for performing diagnostic wedge resections has been lowered by the introduction of video-assisted techniques. Yet although these factors make it easier to proceed quickly to resection, for patients with benign conditions, they incur cost and morbidity that might have been avoided had a course of observation been chosen instead.

Fundamental tumor biology suggests that delay between presentation and resection might have a minimal effect on prognosis. Lung tumors large enough to be

detected by means of standard chest radiography (≥1 cm in diameter) contain approximately 10^9 cells and therefore have undergone approximately 30 cell doublings.[2] Studies of tumor biology reveal that doubling times for squamous cell carcinomas and adenocarcinomas are approximately 88 and 161 days, respectively.[2] Thus even lung cancers barely detectable by means of chest radiography might have been present for as long as 7 years. The increased sensitivity of spiral computed tomography (CT) decreases the detection threshold to approximately 5 mm in diameter, but this translates into a saving of only 3 doubling times or 10% of the tumor's life span. Hence there is considerable opportunity for the cancer to disseminate before its detection by even the most sensitive of current technologies.

Tumor size represents a convenient marker for disease progression, but for an individual patient, growth of his or her tumor during a period of observation before surgical intervention might have little clinical significance. It is known that patients with larger tumors (≥3 cm in diameter) fare worse than do patients with smaller tumors,[3-5] but it is not known whether the prognosis for an individual patient worsens if his or her small tumor is allowed to grow during a brief period of observation. Tumor dissemination, not tumor size, is the primary determinant of the curative potential for surgical intervention. For a delay in intervention to be harmful, it must permit dissemination and not just growth of the primary tumor. Recent evidence demonstrates that early metastases are not detectable with standard pathologic examination.[6,7] Thus early dissemination is unlikely to be apparent to the pathologist, and patients with early dissemination will be classified as having pathologic early stage disease. Presumably, these are the patients who will die of recurrent cancer despite "curative" operations. If a delay in surgical intervention permits tumor dissemination, then the effect of delay on prognosis should be most apparent for patients with resected pathologic early stage disease.

The goal of this study was to determine whether the length of time between detection and resection of early stage lung cancers correlates with survival.

Material and Methods

The Committee on Human Research of the University of California, San Francisco, and the Institutional Review Board of the San Francisco VA Medical Center reviewed and approved this study. Records from the San Francisco VA Medical Center from 1989 to 1999 were reviewed. Charts of patients who underwent surgical intervention for pathologic stage I or II NSCLC were abstracted for patient age, race, sex, medical history, date of presentation, date and type of surgical treatment, pathologic stage, cause of death, and date of death or last follow-up. Date of presentation was defined as the earliest date at which the pulmonary lesion could have been identified. The preoperative interval (delay) was defined as the time between presentation and the operation.

Survival was defined in 2 ways. First, it was defined as the time from surgical intervention to death or last follow-up. This method is the cleanest from a statistical standpoint, but it introduces the possibility of lead-time bias: the survival of patients with long delays between presentation and surgical intervention does not include the preoperative waiting time and therefore might be artificially short. To address this issue, we also performed landmark analyses in which time is counted from the date of presentation, but the length of delay is assessed at a point (landmark) a fixed number of days after presentation. For these analyses, patients who died or were censored before the landmark (90 days) are regarded as noninformative.

Kaplan-Meier survival analysis was performed (SAS, version 6.12; SAS, Inc, Cary, NC), and log-rank analyses were used to test for the effect of delay on survival. The effect of delay on survival was first analyzed by using delay as a single, continuous variable. In a second analysis patients were divided into 2 groups on the basis of the length of preoperative delay (≤90 days or >90 days), and survival between the groups was compared. For analysis of disease-specific survival, patients who died from causes unrelated to their lung cancer were censored at the time of death.

Results

Patient Characteristics

From 1989 through 1999, 84 patients underwent surgical intervention for pathologic stage I or II NSCLC, 46 within 90 days of presentation and 38 at least 90 days after presentation (Table 1). Median age at presentation was 66 years, and 95% of the patients were men. Thirty-eight percent had hypertension, 30% had coronary artery disease, and 54% had emphysema. Fifty-six (66.7%) patients had right-sided cancers. There were 84 operations in 84 patients. Right upper lobectomy was the most common procedure, and 14 patients underwent pneumonectomy. Adenocarcinomas were slightly more common than squamous cell carcinomas, and the remaining tumors were large cell carcinomas. Fifty-nine (70%) patients had pathologic stage I disease.

Preoperative Delay

Time from detection of the pulmonary lesion to surgical intervention ranged from 1 to 641 days, with a median of 82 days and a mean of 126 days. Delay was greater than 200 days for 14 patients. Of these, 4 had no documentation of the reason for delay. For the remaining 10 patients, delay was attributed to treatment of comorbidities, patient decision making, retrospective detection, observation with serial films, and delays in transferring patients and patient information from referring hospitals.

Survival Analysis

Median follow-up after surgical intervention was 3.3 years (range, 5 days-11.9 years). Forty-two (50%) patients were alive at the time of analysis. Of the 42 patients who died, 21 (50%) died of documented metastatic lung cancer. One patient died from metastatic adenocarcinoma that might have arisen from either his lung or his colon cancer. There

TABLE 1. Patient characteristics by duration of preoperative delay

	<90-d delay	>90-d delay
Total No.	46	38
Sex		
Male	43	37
Female	3	1
Median age (y)	63	68
Tumor location		
Right	33	23
Left	13	15
Procedure		
Wedge	1	5
Lobe	40	24
Pneumonectomy	5	9
Histology		
Adeno	20	20
Squamous	21	4
Large cell	5	14
Pathologic stage (AJCCS)		
1A	11	17
1B	18	13
2A	2	1
2B	15	7
Comorbidity		
Emphysema	26	19
CAD	12	13
Hypertension	16	16
DM	6	8
Other malignancy		
GI	4	4
GU	4	4
H&N	3	3
Lung	2	0
Other	3	3

AJCCS, American Joint Committee on Cancer Staging; *CAD*, coronary artery disease; *DM*, diabetes mellitus; *GI*, gastrointestinal; *GU*, genitourinary; *H&N*, head and neck.

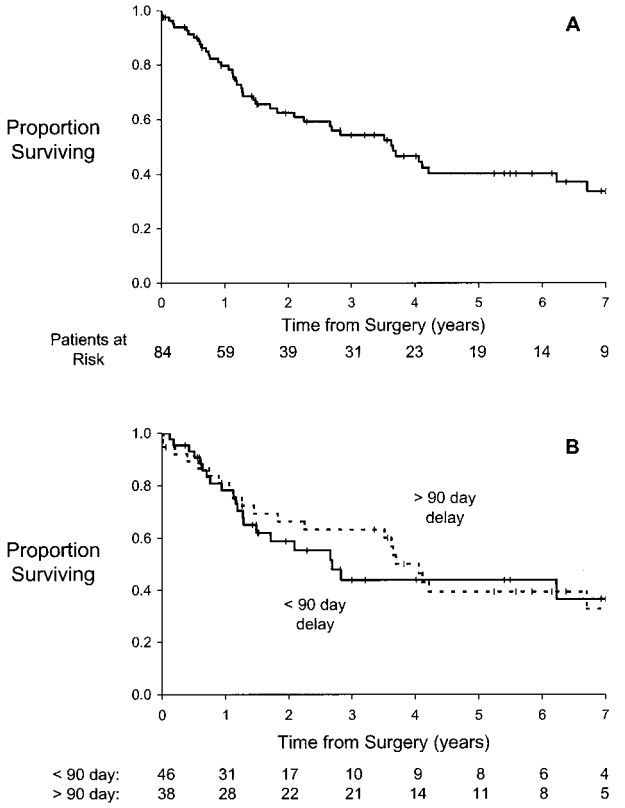

Figure 1. Overall survival from the date of surgical intervention. A, Survival for all patients as a single group: correlation between survival and preoperative delay as a continuous variable was not significant ($P = .54$; hazard ratio of 1.06 and 95% CI of 0.87-1.30 for a 90-day increment in delay). B, Survival for patients grouped by duration of preoperative delay (*solid line*, <90 days; *dashed line*, >90 days): difference by log rank was not significant ($P = .78$).

were 3 perioperative deaths. Two (2.4%) patients died within 30 days of surgical intervention: one from intraoperative bleeding and one from respiratory failure on postoperative day 4. One patient died from respiratory failure 44 days after surgical intervention. Eighty-three percent (35/42) of the patients who died did so within 4 years of presentation.

Overall 5-year survival was 40%, and median survival was 3.7 years (Figure 1, *A*). Log-rank analysis demonstrated no significant effect of preoperative delay on postoperative survival ($P = .54$). The estimated hazard ratio for a 90-day increment in delay was 1.06 (95% confidence interval [CI], 0.87-1.30). We also carried out an analysis in which delay was dichotomized at 90 days. This time interval is close to the median for our population and also represents a standard waiting time between serial radiographic evaluations of a patient with a low-suspicion pulmonary nodule. We found no significant difference in the postoperative survival between these 2 groups ($P = .78$; Figure 1, *B*).

A landmark analysis was performed in which survival was calculated from the date of presentation instead of the date of surgical intervention to address the potential problem of lead-time bias. With this modification, analysis did not show a significant effect of delay on survival ($P = .66$; Figure 2, *A*). The hazard ratio for failure to undergo an operation by the 90-day landmark was 0.87 (95% CI, 0.47-1.61). Similarly, when preoperative delay was dichotomized, there was no significant difference in survival between the 2 groups ($P = .45$; Figure 2, *B*).

Data were also analyzed by using disease-specific survival as the end point. Patients who died of causes unrelated to lung cancer were censored at the time of death. Five-year disease-specific survival, measured from the date of the operation, was 63% (Figure 3, *A*). The effect of preoperative delay on survival was not significant, either as a continuous variable or when patients were divided into 2 groups on the basis of a delay of 90 days (Figure 3, *B*). Landmark analyses of these data also demonstrated no significant effect.

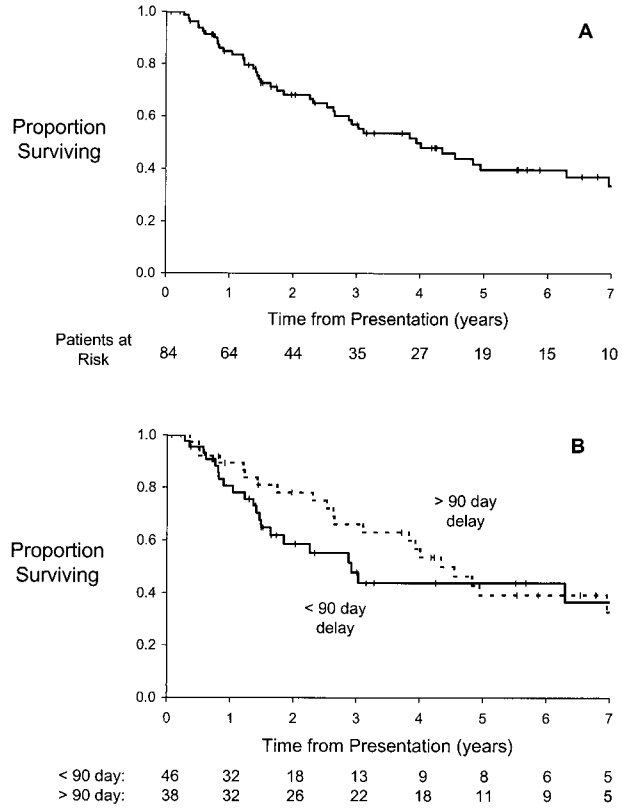

Figure 2. Overall survival from date of presentation. A, Survival for all patients as a single group: correlation between survival and preoperative delay as a continuous variable was not significant ($P = .66$; hazard ratio of 0.87 and 95% CI of 0.47-1.61 for a 90-day increment in delay). B, Survival for patients grouped by duration of preoperative delay (*solid line,* <90 days; *dashed line,* >90 days): difference by log rank was not significant ($P = .45$).

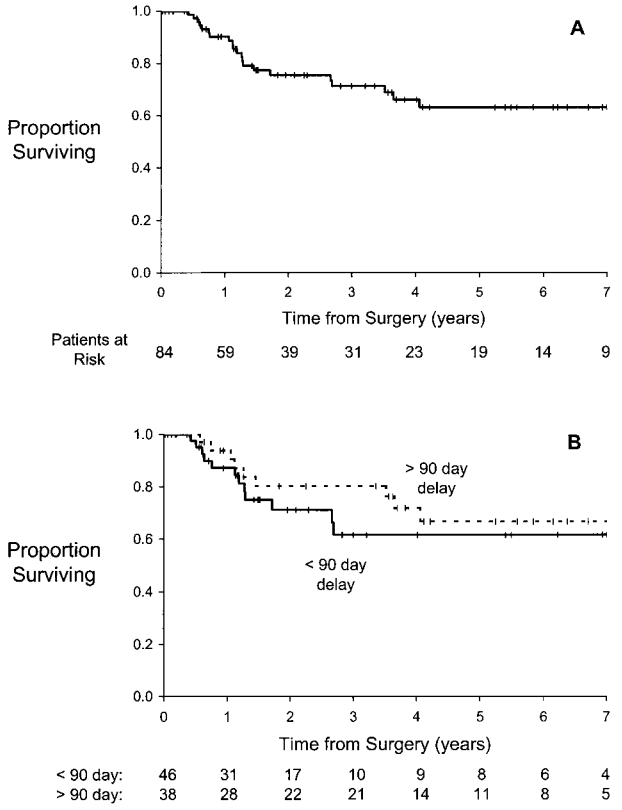

Figure 3. Cancer-related survival from the date of surgical intervention. Patients who died from causes other than lung cancer were censored at the time of death. A, Survival for all patients as a single group: correlation between survival and preoperative delay as a continuous variable was not significant ($P = .64$). B, Survival for patients grouped by duration of preoperative delay (*solid line,* <90 days; *dashed line,* >90 days): difference by log rank was not significant ($P = .23$).

Discussion

Patients with known or suspected early stage lung cancer should proceed expeditiously through evaluation, staging, and surgical intervention, but for some patients with an indeterminate lung nodule, repeat imaging 3 months later is an acceptable alternative. The increasing use of spiral CT[8] to screen for early lung cancers will dramatically increase the number of patients found to have indeterminate pulmonary nodules, and the appropriate management of these patients is unclear. The desire to avoid delay in therapy prompts some clinicians to advocate resection of these nodules soon after their detection, but it is questionable that such an aggressive approach will improve survival. Furthermore, this strategy will expose many patients with benign disease to the expense and morbidity of unnecessary testing and operations. Concern that delay in surgical intervention might worsen prognosis is also a factor in some clinicians' resistance to the use of neoadjuvant therapy for patients with early stage lung cancer.

Studies of tumor biology indicate that even the smallest lung cancers have been present for many years before becoming clinically apparent. How critical, then, is it to proceed quickly to surgical intervention, and how detrimental is it for there to be a relatively brief period of delay associated with either observation or preoperative therapy? A large prospective randomized trial would be necessary to conclusively answer this question, but such a trial is unlikely. As an alternative, we chose a retrospective analysis of all patients who underwent operations for early stage NSCLC at a single institution. This population experienced a broad range of delay between when the tumor first became apparent and when it was resected. Our results do not demonstrate that an increasing interval between detection and surgical intervention affected survival.

The patients included in this series are similar in many respects to the larger population of all patients with lung cancer. Smoking history, age, histology, and lobar distribu-

tion of disease are all representative of the population at large. Consistent with a VA population, however, 95% were men. Survival also differed from the expected value and was only 40% at 5 years, which is lower than anticipated for a mixture of patients with stage I and II disease. This probably reflects the high incidence of significant comorbidity in the veteran population: 39 (46%) patients had a second malignancy, and only 21 of the 42 deaths were attributable to documented recurrent lung cancer. When deaths unrelated to lung cancer are censored, long-term survival compares favorably with historical results.

Christensen and colleagues[9] also examined the effect of delay in therapy on survival. They collected retrospective data for 172 patients and found that the time from presentation to initiation of treatment was longer for those with stage III or IV disease than for those with stage I or II disease. From this, they concluded that delay in therapy increased the risk of disease progression. However, it is not clear that disease stage at presentation was comparable between the 2 groups. Longer delays in the advanced-stage group might be attributable to a more extensive diagnostic and metastatic work-up and therefore might be the result and not the cause of the advanced stage. Importantly, Christensen and colleagues found that median delay for patients with stage I or II disease was 3 months, which is similar to the median delay for patients in our series.

Others have approached the question of the effect of preoperative delay by using tumor size as a surrogate for time. The size criterion for distinction between T1 and T2 tumors implies that larger tumors carry a worse prognosis, and hence some argue that delaying surgical intervention while the patient's tumor grows risks worsening prognosis. Koike and associates[10] reviewed 496 patients who underwent operations for clinical stage IA NSCLC. They found that tumors 2.0 cm or less in diameter were associated with a better prognosis than tumors of 2.1 to 3.0 cm in diameter. In contrast, Patz and coworkers[11] concluded from their retrospective series of 510 patients with pathologic stage IA disease that tumor size did not correlate with survival. Regardless, these results might not be applicable to the effect of a prolonged preoperative interval on prognosis for individual patients. For this extrapolation to be valid, two assumptions must be true. First, larger tumors must have grown from smaller ones, and second, when the larger tumors were of equivalent size to the smaller ones, they must have had equivalent biologic behavior. Although the former assumption is certainly true, the latter likely is not: larger tumors might present as larger tumors because they are more aggressive and not simply because they are older. Furthermore, any survival analysis in which these groups are compared is subject to lead-time bias: if the larger tumors are older, then the patients' survival after surgical intervention necessarily will be shorter.

There are important limitations to this retrospective analysis. First, the inclusion of only patients with pathologic early stage disease might have excluded from analysis precisely those who suffered most from a delay: patients who progressed from early to advanced stage while awaiting surgical intervention. Although this possibility cannot be excluded, we believe that including only patients with early stage disease is the most effective way to concentrate on patients who might have experienced the transition from truly localized to disseminated disease. Early metastases should be pathologically occult. Recent work with detection of micrometastases[12] and occult disease[3,13,14] support the hypothesis that disease progression involves dissemination of tumor cells well before metastases are apparent by means of standard pathologic examination. Therefore standard pathology for patients with early tumor dissemination is unlikely to detect this early phase of metastasis, and patients who experienced the transition from localized to disseminated disease would continue to have pathologically early stage disease for some time.

Limiting a review to only patients with pathologically early stage disease does include patients whose primary tumor might have progressed from T1 to T2 by virtue of invasion of the visceral pleura. This event should be considered a risk factor for dissemination, and its effect on survival, if any, should be reflected in a study of patients with pathologic early stage disease.

A second limitation of this study is sample size. Our study is small, and the 95% CIs for calculated hazard ratios are broad. This indicates that the lack of statistical significance might reflect a type II error. With 42 deaths and 42 patients alive or lost to follow-up, our study has an 80% power to detect a hazard ratio of 2.38. To illustrate this value, if overall survival is 40%, then survival in the high-risk and low-risk groups must be 55% and 24%, respectively, for the difference to achieve statistical significance. For this study to have sufficient power (80%) to detect a hazard ratio of 1.5 (overall survival, 40%; low risk, 47%; high risk, 32%), a minimum of 166 patients in each group, with complete follow-up, is required.

Surgical intervention remains the most effective therapy for patients with early stage lung cancer, indicating that resection must deprive localized tumors of the opportunity to disseminate, but survival statistics, tumor biology, and studies of occult disease suggest that a reasonable delay in time to surgical intervention might not affect tumor dissemination. Our series is small, and similar analyses of larger groups of patients are needed, but our results should be thought provoking and hopefully will stimulate us to reconsider the value of observation as a diagnostic tool. Renewed interest in screening[15-19] and widespread use of spiral CT will identify many patients with indeterminate pulmonary nodules. This will make it increasingly important for us to

be willing to forego an expensive diagnostic work-up and prompt resection in favor of confident reassurance and prudent observation. In this regard the novel use of computer algorithms to assess small changes in tumor volume over relatively brief periods of time is an exciting development.[20]

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Discussion

Dr John Benfield *(Los Angeles, Calif).* Dr Quarterman and colleagues reviewed their 9-year experience with 84 patients with stage I and II lung cancer whose median follow-up was about 3.6 years to assess whether delays between detection and resection influenced outcomes. It is not surprising that outcomes were independent of the alacrity of definitive therapy in light of what we know about cancer biology. However, such observations have on occasion been carried to absurdity, with the contention that treatment is only a passing event in the natural history of the neoplasm, and in clinical practice each of us can cite many harmful examples of procrastination. Two things are important: in some cases resection is the only treatment that is curative, and in all cases patients and their families view the diagnosis of lung cancer as an emergency. Dr Quarterman's findings support the practice of reassuring anxious patients and their families to the effect that a scheduled delay between diagnosis and treatment will do no harm. However, I believe it would be pushing the clock back decades, and a pity, if Dr Quarterman's findings were used to justify procrastination. Judicious observation has always been an option that each of us recommends occasionally, but in my judgement resection of an indeterminate lung lesion remains the most conservative management that can be recommended for an indeterminate lung lesion.

In their thoughtful article Quarterman and associates appropriately discuss the limitations of their report. I want to add the limitation that their selection of 82 days as the cutoff point between timely and delayed resection is understandable but artificial. In practice, about 10 days should be the cutoff point between delayed and prompt treatment. Having said this, I readily concede that it is unlikely that a different cutoff point would have changed their findings. Much more important is our limited and still primitive ability to assess the behavior of cancers *(ie, tumor biology)*.

The keys to predicting the behavior of cancers and to having data on which to base rational and effective systemic treatments surely lie in the genomic area. This is illustrated in embryonic fashion by many ongoing studies of oncogenes and tumor suppressor genes and gene therapy. The future is exciting, and I am very happy for young surgeons who are at the beginning of their research careers.

I predict that some years from now Dr Quarterman and colleagues will be reporting about time intervals from detection to resection only in passing. Instead, they will correlate cytogenetic data, tumor markers, and immunologic modifiers with treatment outcomes. The work-up of each patient will include assessment of genetic profiles of his or her cancer. Eventually, we will also have measures of host resistance of each patient. Armed with such information, multimodality treatment planning, often including surgical intervention, will become more effective than today's management.

This has been a useful report, particularly because it is the beginning of larger studies, presumably in the framework of cooperative trials. Dr Quarterman, would you please tell us what you have in mind and how far you have progressed toward the extension of your work?

Dr Quarterman. Thank you. Our current plan is to set up collaborations with other VA medical centers. The VA database is very advantageous because there are several centers within it. Also, there is a tumor registry with centralized information from

which we can begin analysis. Third, VA centers are beginning to have a more regimented documentation and charting process, which will make abstracting data and interpreting data easier.

We are also starting up some studies in molecular biology to begin to evaluate tumor markers for staging and possible prediction of prognosis, with the expectation that in the future, that type of information will make the question of preoperative delay unnecessary.

Dr Steven Guyton *(Seattle, Wash).* I am concerned about your point of time for patient selection because you have identified a group of patients with good prognoses. Did you make any attempt to go back and find patients who presented with pulmonary nodules who then turned out to have more advanced disease?

Dr Quarterman. Yes. We decided to exclude patients who ended up having pathologic stage III or IV disease because our interest was in evaluating patients who began with localized disease. With the knowledge of tumor biology, it is expected that patients who have disseminated disease with micrometastases would have such metastases that are not detectable pathologically, and our interest was in picking up patients who started out with localized disease and progressed to disseminated disease. It was believed that if we evaluated patients who had stage III or IV disease at the time of the operation, it was likely that they began with a disease that was beyond being localized in the first place.

Dr Douglas Wood *(Seattle, Wash).* I think that your article is a valuable one and gives us some justification for the occasional patient that we do observe and for giving some reassurance to those patients. I have just come from a meeting at the National Cancer Institute of screening in lung cancer attended by radiologists, pathologists, and surgeons. The radiologists now believe, and I think that they are right, that the indeterminate nodule is now almost nonexistent and that with the types of CT scans that we have today and the ability to analyze them on the basis of CT criteria and with positron emission tomography imaging, that truly we have the characteristics that we need to determine whether a nodule can be observed or resected. What percentage of the nodules do you think, with the imaging that we have today, are truly indeterminate and would fall in this category that we would follow? I agree with Dr Benfield that the majority of the nodules are interpretable and should be resected.

Dr Quarterman. I think that is a good point, and in fact, most of the nodules that would be detected in this day and age would cause care teams to get further evaluation, and most likely, a very small percentage of them are actually nonmalignant or of no consequence. Nonetheless, I think that our findings continue to bring up the concept of watchful observation and to keep in mind that such a technique is still possibly valid in evaluating nodules, such that instead of going straight to fine-needle aspiration, serial observations with radiographic studies could still be possible without being detrimental to the patients.